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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/234,208	01/20/99	DOHERTY J	49321-1

022504
DAVIS WRIGHT TREMAINE, LLP
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE WA 98101-1688

HM12/0801

EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/234,208	Applicant(s) Doherty et al.
	Examiner Jennifer Hunt	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above, claim(s) *4-7, 11-17, and 21-26* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 8-10, and 18-20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *14*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-3 and 8-10 in Paper No. 12 is acknowledged.

2. Upon further consideration, the examiner has included claims 18-20, drawn to a pharmaceutical composition, with Group I. The examiner further has combined the methods of Group III and IV. Thus the restriction is now as follows:

I. Claims 1-3, and 8-10, and 18-20 drawn to an isolated polypeptide, classified in class 530, subclass 350.

II. Claims 4-7, and 11-13, drawn to DNA, and corresponding host cell transfected with corresponding vector, classified in class 536, subclass 23.5, class 435, subclass 320.1 and 70.1.

III. Claims 14-17 and 21-23, drawn to a method of treating a solid tumor and to a method of targeting a therapeutic agent to a tumor, classified in class 424, subclass 181.1 and 277.1.

IV. Claims 24-26, drawn to a method of determining prognosis of tumor treatment, classified in class 435, subclass 7.1.

A phone call was place to Barry Davidson on 7/3/2001, who maintained the election of Group I, as it is revised.

With regard to the traversal of the original restriction, the traversal is on the ground(s) that the restriction should be drawn to two groups instead of five, that the restriction requirement imposes and undue burden on applicant. Applicant expands this argument to state that the division of a polynucleotide from polypeptide based on differing chemical structure is a "poor excuse" for restriction because the purpose of an oligonucleotide is to express a polypeptide. Applicant adds that the EPO does not separate polypeptide and polynucleotide. With regard to the additional groups, applicant argues that the PTO has improperly divided the claims based on independent claims, and that the inventions of all of the groups could be accomplished by a single broad search. This is not found persuasive because for reasons set forth in the original restriction requirement, the compositions and methods of original Groups III-V are distinct from Group I. A polynucleotide is distinct from a polypeptide, and art that reads on one structure may not read on another. Further distinct issues with regard to patentability distinguish a polynucleotide from a polypeptide. Additionally, the practice of the EPO is not relevant to examination of a US filed case. The EPO is subject to different statues, policies and procedures. Additionally, the claims are not divides based on independent claims, but rather by distinct products and methods. Lastly, the searches for the groups are not co-extensive, and art over one invention would not necessarily anticipate another. And thus for the reasons set forth in the previous restriction requirement, reiterated and expanded above, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-26 are pending in the application. Claims 4-7, 11-17, and 21-26 have been withdrawn from consideration. Claims 1-3, 8-10, and 18-20 are considered herein.

Specification

3. The use of the trademark Herceptin(R), and Brightstar (R) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Further, applicant should conduct a thorough search of the specification to ensure that any additional trademarks are appropriately recited.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 8-10, and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 8-10, and 18-20 are unclear in the recitation of "extracellular domain ECD". It is not clear if the recitation refers to the extracellular domain of "ECD" or if ECD is an abbreviation for extracellular domain. Amending the claim to recite extracellular domain (ECD) would bring favorable consideration.

6. The term "10^8" in claims 1-3, 8-10, and 18-20 is a relative term which renders the claim indefinite. The term "10^8" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, because no units are given, the metes and bounds of 10^8 cannot be determined.

7. Claims 3 and 10 contain the trademark/trade name HERCEPTIN (R). Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the 4D5 monoclonal antibody and, accordingly, the identification/description is indefinite. Use of the generic terminology would likely bring favorable consideration.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 8, 9, and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 8, 9, and 18-20 are broadly drawn to a polypeptide of almost any size comprising a sequence which minimally contains fragment of SEQ ID NO: 1 or 2. Thus the claims are drawn to a peptide of almost any size which is only defined by a small number of amino acid resides, and therefor are drawn to a large genus of molecules. In the case of small identified amino acid residues claimed with open language, the genus of the polypeptides comprising a partial sequence encompasses a variety of subgenera with widely varying attributes. The specification discloses only the structural features of two species, the polypeptide of SEQ ID NO: 1 and 2. The specification lacks information to lead one of ordinary skill in the art to understand that the applicant had possession of the broadly claimed genus of polypeptides at the time the instant application was filed. Applicant is referred to the guidelines 112, first paragraph, published in the Official gazette and also available on www.uspto.gov.

10. Claims 1-3, 8-10, and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide comprising SEQ ID NO:1, or SEQ ID NO:2, does not reasonably provide enablement for any isolated peptide having from about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids from SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification. 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to any isolated peptide which has about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2. It is noted that claims to not require that these amino acids be contiguous.

The specification discloses a single isolated polypeptide, p68HER-2, which comprises a modified extension of the art known p185HER-2, which is a 79 amino acid peptide, named ECDIIIa. Both p68HER-2 and ECDIIIa bind to p185HER-2 and do not activate signal transduction. Further, the specification provides no objective evidence that any other isolated

polypeptides which would function as ECDIIIa and p68HER-2 do. Disclosure of a single fragment(ECDIIIa), and peptide which comprises that fragment (p68HER-2), which bind to p185HER-2 is insufficient support under 35 U.S.C. 112 first paragraph for claims which encompass any isolated polypeptide which binds to the ECD of HER-2, provided that it contains at least 50 etc. (Non-contiguous) amino acids from SEQ ID NO: 1 or 2. The courts have held that:

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based In some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not In compliance with the first paragraph of U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill In the art; In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement In the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; In cases involving unpredictable factors, such as chemical reactions and physiological activity, scope of enablement varies inversely with

degree of unpredictability of factors involved."In re Fisher 427 F.2d 833, 166 USPQ 18 (CCPA 1970)

Further, the claims as recited encompass numerous amino acid variants. The following is set forth to establish the unpredictability of amino acid substitutions in protein function: Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of

aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3).

Thus because the quantity of experimentation necessary would be very high and the predictability of the art is low, the amount of direction or guidance presented in the specification and the working examples in the specification are limited, and the claims are broadly drawn, one of skill in the art would not be able to make the invention commensurate in scope with the claims.

11. Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to any isolated peptide which has about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2. It is noted that claims to not require that these amino acids be contiguous. Further, claims are drawn to any such peptide which binds to a site other than that bound by HERCEPTIN.

The specification provides no guidance or objective evidence that the claimed isolated polypeptide binds to a site other than that bound by the HERCEPTIN antibody. Further, applicant has given no guidance (beyond a generic teaching) as to what the HERCEPTIN antibody refers to, or where that antibody binds. The instant disclosure fails to clearly set both where the antibody binds, how the antibody is produced, or any of the structural or functional information which would be necessary to produce the antibody, or determine how to produce a polypeptide which binds to a distinct site. Further, there is no evidence or guidance that the ECDIIIa or p68HER-2 peptides themselves bind to a site other than the one bound by the HERCEPTIN antibody.

Thus because the quantity of experimentation necessary would be very high and the predictability of the art is low, the amount of direction or guidance presented in the specification

is low, there are no working examples, and the claims are broadly drawn, one of skill in the art would not be able to make the invention commensurate in scope with the claims.

12. Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to any isolated peptide which has about 50-79 or 69-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 300-419 or about 350-419 amino acids taken from SEQ ID NO:2. It is noted that claims to not require that these amino acids be contiguous. Further, claims are drawn any such peptide which functions as a pharmaceutical composition.

Additionally, claims recite methods which encompass the experimental and unpredictable field of in vivo therapy for mammals having a condition characterized by over expression of Her-2 receptor or cancer. Articles by Dillman et al. (*J Clin Onco Vol 12, No 7, pages 1497-1515, 07/1997)* and *Dermer (BIO/TECHNOLOGY, Vol 12, page 320, 03/1994*) are cited in order to establish the general state of the art and the level of predictability of in vivo therapy . Dillman et al, while discussing observations related to antibody therapy, teach that "on the negative side is the observation that clinical results do not necessarily improve when humanized chimeric antibodies are used in humans, to spite encouraging in vitro results in CDC

or ADDC" (page 1506, col 2 paragraph 3). Dermer teaches that "What is significant in culture, for example immunotherapy's killing power or the transformation of 3T3 cells by a mutated proto-oncogene, simply does not have the same significance for cells in vivo."

Those of skill in the art recognize that in vitro assays are generally useful to screen the effects of agents on target cells. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo experiment as compared to the very narrowly defined and controlled conditions of an in vitro assay does not permit a single extrapolation of in vitro assays to mammal or human therapeutic with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Further a therapeutic agent must accomplish several tasks to be effective: it must be delivered into circulation and interact at the proper site of action, and it must do so at a therapeutic concentration and remain effective for a sufficient period of time. In vitro assays cannot duplicate the complex conditions of in vivo therapy. In assays, the agent is in contact with the cells during the entire exposure period, whereas in the case of in vivo therapy, exposure at the target site may be delayed or insufficient.

Further, applicant has demonstrated no anti-tumor function of the ECDIIIa or p68HER-2 polypeptides themselves, nor the additional enumerous peptides encompassed by the broadly drawn claims. Applicant's disclosure shows that the ECDIIIa or p68HER-2 polypeptides bind to the p185HER-2 polypeptide, and do not activate signal transduction, but applicant has provided

no further guidance or evidence of anti-tumor activity, or even why one of skill in the art would expect such a function to induce anti-tumor activity.

The field of cancer therapy is well established to be highly complex and unpredictable, and absent specific guidance or objective evidence, one of skill in the art would not expect a polypeptide to have an anti-tumor function.

Thus because the quantity of experimentation necessary would be very high and the predictability of the art is low, the amount of direction or guidance presented in the specification and the working examples in the specification are limited, and the claims are broadly drawn, one of skill in the art would not be able to make the invention commensurate in scope with the claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

July 15, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600